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Part 2: Synopsis of B-lymphocyte targeted therapy of ANCA-associated vasculitis

J.M. Golbin, U. Specks

Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN, USA.

Jason M. Golbin, DO, Ulrich Specks, MD.

Please address correspondence to: Ulrich Specks, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

E-mail: specks.ulrich@mayo.edu

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Rationale for the use of rituximab in ANCA-associated vasculitis (AAV)

Rituximab (RIT) is a chimeric monoclonal antibody directed against CD20, a transmembrane cell-surface protein expressed selectively on B-lymphocytes. B-lymphocyte depletion caused by RIT therapy has proven efficacy in non-Hodgkin's B-cell lymphoma. In 1999, a patient with lymphoma treated with RIT experienced improvement of generalized severe arthritis symptoms. This clinical observation initiated an era of investigation of B-lymphocyte depletion as therapy of a variety of autoimmune diseases, including those previously thought to be largely T-cell mediated (1). The first use of RIT in a patient with chronically relapsing severe refractory Wegener's granulomatosis (WG) was based on the observations that (a) higher frequencies of activated peripheral blood B-cells are associated with disease activity and severity, (b) the most effective agent for WG (cyclophosphamide) has profound effects on B-cells, and (c) on the hypothesis that anti-neutrophil cytoplasmic antibodies (ANCA) play a significant role in disease pathogenesis and that ANCA are produced by short-lived plasma cells, the progeny of antigen-specific B-cell precursors (2).

Remission-induction of AAV with rituximab and glucocorticoids

Following RIT therapy the index patient experienced a long-lasting stable remission off glucocorticoids (2). This success was reproduced in additional 10 patients treated with RIT on a compassionate use basis, and again in 10 patients with refractory AAV in a prospective open-label pilot trial conducted (3, 4). All patients achieved a sustained remission and discontinued glucocorticoids, demonstrating that selective targeting of B-lymphocytes represents a promising treatment option for patients who fail to respond satisfactorily to cylcophosphamide or do not tolerate this agent (3, 4). Moreover, this initial experience suggested that RIT is well tolerated in AAV. A number of other centers have subsequently published similar results (summarized in Table I).

Repeated use of rituximab and long-term B-cell depletion

To date, two reports have emphasized the repeated use of RIT in AAV. Stasi *et al*. reported successful management of 10 patients over a median of 33.5 months (5). Nine patients achieved complete and one a partial remission; 7/10 remained in remission for the entire follow-up period. In the three patients who suffered relapses, remission was restored by retreatment with RIT without significant adverse effects. Smith *et al*. demonstrated similar results in 11 patients in AAV; 9 achieved complete remission, one partial remission, and one failed treatment (6). Of the 10 responders, 4 suffered 5 clinical relapses, all of which were successfully retreated with RIT. Our long-term experience in 28 patients who received 2-5 courses of RIT over a mean of 35 months (range 7-76) confirms the efficacy and safety of repeated RIT use and further demonstrates its potential for remission maintenance (7).

Rituximab treatment for Churg-Strauss syndrome

Four patients with Churg-Strauss syndrome have been successfully treated with RIT; three were described as case reports (8, 9), and one reported in the broader context of AAV by Smith *et al*. (6). In all four patients RIT-induced remission was associated with a reduction of eosinophil counts. One patient was retreated three times for clinical relapses, with resolution of symptoms with each re-treatment. Based on these encouraging early reports, the efficacy of RIT in Churg-Strauss syndrome merits further investigation.

Adverse effects of rituximab therapy for AAV

RIT appears to be well-tolerated by most patients. However, infusion-related adverse events – typically limited to a patients' first infusion – are reported by up to 10% of subjects. These reactions are usually mild and do not preclude completion of the infusions. Interestingly, the concomitant use of high-dose glucocorticoids during the treatment phase with RIT may help prevent some RIT-related reactions. Reactivation of

Table I. Overview of published studies of rituximab in ANCA-associated vasculitis.

Series type	Reference	Patient #/ Diagnosis	RIT doses (pt#-#doses x amount)	Concomitant drugs	Remission	Follow-up (months)	Relapse(#)
Compassionate use	3	10 WG 1 MPA	11-4x375 mg/m^2	11 Prednisone	11 complete	14 median	2
Open label	4	10 WG	10-4x375 mg/m^2	10 Prednisone	10 complete	12 median	1
Prospective	Eriksson P. J Int Med 2005;257: 540-48	7 WG 2 MPA	6-4x500 mg 2-2x500 mg 1-4x375 mg/m^2	4 MMF 1 MMF+SIR 1 AZA 2 CYC 1 None	8 complete 1 partial	19 median	2
Case series	10	3 WG	2-4x375 mg/m^2 1-1x375 mg/m^2	Unknown	3 complete	12 median	3
Open label	8	8 WG	8-4x375 mg/m2 q4 weeks	5 CYC 2 MTX 1 MMF	2 complete 1 partial 5 failed	18 median	0
Retrospective	Gottenberg JE, et al. Ann Rheum Dis 2005;64:913-20	2 WG	1-3x375 mg/m^2 1-15x375 mg/m^2	1 MP 1 MTX+MMF	1 complete 1 failed	16.5 median	0
Prospective Long-term	5	8 WG 2 MPA	10-4x375 mg/m^2	Prednisone	9 complete 1 partial	33.5 median	3
Prospective Long-term	6	5 WG 5 MPA 1 CSS	11-4x375 mg/m^2	11 CYC (1 dose)	9 complete 1 partial 1 failed	23 median	5

WG: Wegener's granulomatosis; MPA: microscopic polyangiitis; CS: Churg Strauss syndrome; RIT: rituximab; MMF: mycophenolate mofetil; SIR: sirolimus; AZA: azathioprine; CYC: cyclophosphamide; MTX: methotrexate; MP: methylprednisolone.

latent viral infections have been reported in patients treated with RIT, but even its repeated use in AAV does not seem to portend a higher risk for infections than other more commonly used immunosuppressive agents. However, definitive conclusions about the safety of RIT in AAV are premature as the number of reported cases is too small to detect a potential increased frequency of rare adverse events, and a randomized blinded comparison of RIT to standard immunosuppression in AAV is still ongoing.

Open questions about RIT treatment in AAV

A prospective, multi-center, double-blind, placebo-controlled phase II/III trial of RIT for ANCA-associated vasculitis (RAVE-trial, www.clinicaltrials.gov) is being conducted in 200 patients to determine the efficacy and safety of RIT in AAV and whether RIT can replace CYC for remission induction. This trial also addresses a variety of other important clinical and pathomechanistic questions. Importantly, individual genetic, pharmacokinetic, or disease phenotype determinants of a variable clinical response also need to be identified. For instance, it is well recognized that the duration of B-cell depletion varies widely between 4 and 18 months after a treatment course with RIT. Polymorphisms of Fc-γ-receptors, ethnic differences and degrees of proteinuria have all been suggested as potential factors affecting the efficacy in SLE and other autoimmune diseases. Furthermore, in WG the resolution of granulomatous lesions after RIT therapy may be more protracted than that of disease manifestations caused by capillaritis (10, 11). Aries *et al*. found granulomatous lesions, particularly retro-orbital disease, to be resistant to RIT therapy in 5/8 patients (11). This study also raises the question about the most appropriate dosing regimen, as it is the only report of monthly RIT application, contrasting with the weekly dosing regimen used in the majority of AAV patients (Table I). Furthermore, it remains unclear whether the "lymphoma regimen" of four weekly infusions of 375 mg/m^2 of RIT is essential for efficacy in AAV, or whether similar results can be achieved with two infusions of 1 g (not weight-adjusted). Preliminary data from a British registry presented at this meeting indicate no significant difference in duration of B-cell depletion or relapse-free survival between these two regimens (David Jayne, personal communication).

Other future approaches to target B-cells

New *humanized monoclonal anti-CD 20 antibodies* from a variety of commercial sources are in early clinical trials for lymphoma and autoimmune disease. These agents may become available for investigations in AAV soon.

B-lymphocyte stimulator (BLyS), also known as *B-cell activating factor* (BAFF), is a member of the TNF-ligand superfamily, plays a critical role in B-cell maturation and appears to inhibit B-cell apoptosis. BLyS has

been found to be elevated in a variety of autoimmune diseases including WG (12). Furthermore, serum BLyS levels increase significantly following therapeutic B-cell depletion, and remain elevated until B-cell reconstitution (13). Consequently, it is conceivable that anti-BLyS therapies applied following RIT could provide synergistic effects in autoimmune diseases.

Epratuzumab is a humanized monoclonal antibody directed against CD22, which is another surface receptor expressed selectively on B-cells. An open-label pilot trial of 14 patients with active SLE suggested efficacy with > 70% of patients experiencing a > 50% improvement of disease scores (14). The drug was tolerated well. This agent may also merit further investigation in AAV.

Conclusion

Preliminary data indicate that B-cell depletion with rituximab appears to be an effective and safe mechanism-based treatment approach for remission induction and remission maintenance in refractory AAV. Repeated courses of rituximab appear to be equally effective, and prolonged B-cell depletion has been associated with surprisingly few infections. Whether B-cell depletion should become first-line therapy for newly diagnosed AAV patients remains under investigation.

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